

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER for: 019593, S28**

**CLINICAL PHARMACOLOGY and  
BIOPHARMACEUTICS REVIEW(S)**

OCT 26 1998

## Clinical Pharmacology and Biopharmaceutics Review

NDA: NDA 19-090/S-037; ZANTAC<sup>®</sup> Injection  
NDA 19-593/S-028; ZANTAC<sup>®</sup> Injection Premixed  
NDA 18-703/S-056; ZANTAC<sup>®</sup> 150/300 Tablets, USP  
NDA 19-675/S-020; ZANTAC<sup>®</sup> Syrup, USP  
NDA 20-095/S-007; ZANTAC<sup>®</sup> 150/300 GELDose Capsules  
NDA 20-251/S-006; ZANTAC<sup>®</sup> 150 EFFERdose Tablets and Granules

Active Ingredient: Ranitidine hydrochloride

Submission Date: 11/13/1998

Sponsor: Rhône-Poulenc Rorer Pharmaceuticals Inc.

Stamp Date: 11/16/1998

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Draft Review Dates: 5/19/1999,  
7/29/1999, 10/26/1999

Type of Submission: Labeling Revision for Use in Pediatrics

Final Review Date: 10/26/1998

### Synopsis

Ranitidine is an H<sub>2</sub>-receptor antagonist approved as both intravenous and oral forms for the treatment of active gastric and duodenal ulcers (PUD), maintenance therapy for gastric and duodenal ulcers, pathological hypersecretory conditions, gastroesophageal reflux disease (GERD), and acute and maintenance therapy for erosive esophagitis. The oral dosage forms include tablets, syrup, GELDose capsules and EFFERdose tablets and granules, which are all considered bioequivalent. Ranitidine is about 50% absorbed after oral administration and it has a half-life of 2-3 hrs in subjects with normal renal function. It is primarily eliminated as unchanged drug in the urine.

On December 13, 1996, the Firm submitted a supplement to NDAs 18-703, 19-090, 19-593, 19-675, 20-095 and 20-251 to support the use of ZANTAC<sup>®</sup> (all marketed forms) for the treatment of active gastric and duodenal ulcers, GERD and erosive esophagitis in the pediatric population. The pediatric population is defined as follows: neonates (birth up to 1 month), infants (1 month up to 2 years), children (2 years up to 12 years) and adolescents (12 years up to 16 years). The draft labeling was revised by the Agency in accordance with the 1994 FDA guidance for Industry on the Content and Format for Pediatric Use Supplements and with 21 CFR 201.57 (f) (9) (iii) and (iv), and includes additional pharmacokinetic, pharmacodynamic and safety information specific to pediatric patients. On December 16, 1997, the Agency found the supplements to be approvable provided the Firm incorporates labeling comments suggested by the Agency into the package insert.

This submission represents an annotated, marked-up version of the draft labeling that has been revised by the Firm in accordance with the provisions outlined in the Agency approvable letter (see attachment).

### Recommendations

The proposed Zantac labeling providing for the use of Zantac injections in the pediatric population and supported by supplemental NDAs 19-090 and 19-593, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of

Pharmaceutical Evaluation II) and is found to be approvable, provided the Firm makes the appropriate correction to table 1, so that the value of CLp (ml/min/kg) for children in intensive care (1 day - 12.6 yrs) is changed from 11.7 to 10.2, as reported in *Rylance*. 1987 (see attachment).

The proposed Zantac labeling providing for the use of Zantac oral formulations in the pediatric population and supported by supplemental NDAs 18-703, 19-675, 20-095 and 20-251, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be approvable.

.IS\ [REDACTED]

10/26/99

Suliman I. Al-Fayoumi, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader

FT initialed by David Lee, Ph.D., Team leader

.IS\ [REDACTED]

10/26/99

cc: HFD-180: NDA 19,593 (1x); DIV FILE (1x); AKACUBA (1x); DLEE (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

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**ZANTAC Injection (NDA 19-090, NDA 19-593)**

**Proposed Labeling Changes**

1. The following paragraphs in the CLINICAL PHARMACOLOGY section have been changed  
From,

DRAFT LABELING



DRAFT LABELING



To,

DRAFT LABELING



DRAFT LABELING



**DRAFT LABELING****Reviewer Comments:**

The changes made to those paragraphs are acceptable. However, in table 1, CLp (ml/min/kg) for children in intensive care (1 day - 12.6 yrs) needs to be changed from 11.7 to 10.2, as reported in *Rylance, 1987* (see attachment).

2. In the PEDIATRIC USE section under PRECAUTIONS section, the following sentence,

**DRAFT LABELING**

has been changed to,

**DRAFT LABELING****Reviewer Comments:**

The changes made to those paragraphs are acceptable.

3. Under DOSAGE AND ADMINISTRATION section, the following paragraph has been added.

**DRAFT LABELING****Reviewer Comments:**

The changes made to those paragraphs are acceptable.

ZANTAC non-injectables (ZANTAC Syrup, GELdose Capsules and EFFERdose Tablets and Granules) (NDA 18-703, NDA 19-675, NDA 20-095, NDA 20-251)

**Proposed Labeling Changes**

1. The following paragraphs in the CLINICAL PHARMACOLOGY section have been revised  
From,

**DRAFT LABELING**

DRAFT LABELING



APPEARS THIS WAY ON ORIGINAL



DRAFT LABELING



To,

DRAFT LABELING



DRAFT LABELING



DRAFT LABELING



**Reviewer Comments:**

The changes made to those paragraphs are acceptable.

2. In the PEDIATRIC USE section under PRECAUTIONS section , the following sentence,

DRAFT LABELING



has been changed to,

DRAFT LABELING



**Reviewer Comments:**

The changes made to those paragraphs are acceptable.

3. Under DOSAGE AND ADMINISTRATION section, the following paragraphs have been added,

DRAFT LABELING



DRAFT LABELING



**Reviewer Comments:**

The changes made to those paragraphs are acceptable.

APPEARS THIS WAY ON ORIGINAL



DEC 11 1997

## Clinical Pharmacology and Biopharmaceutics Review

Drug: Zantac® (ranitidine hydrochloride)

NDAs: 18-703/SLR-056; Tablets, 150 and 300 mg  
19-090/SLR-037; Injection  
19-593/SLR-028; Pre-mixed Injection  
19-675/SLR-020; Syrup  
20-095/SLR-007; GELDose® Capsules, 150 and 300 mg  
20-251/SLR-006; EFFERdose® Tablets and Granules, 150 mg

Sponsor: GlaxoWellcome Inc.

Submission Date: December 13, 1996

Submission Type: Pediatric Labeling Supplement

Reviewer: Carol Cronenberger, Ph.D.

### Background/Rationale

Ranitidine is an H<sub>2</sub>-receptor antagonist approved as both intravenous and oral forms for the treatment of active gastric and duodenal ulcers (PUD), maintenance therapy for gastric and duodenal ulcers, pathological hypersecretory conditions, gastroesophageal reflux disease (GERD), and acute and maintenance therapy for erosive esophagitis. The oral dosage forms include tablets, syrup, GELDose capsules, and EFFERdose tablets and granules which are all considered bioequivalent. Ranitidine is about 50% absorbed after oral administration and it has a half-life of 2-3 hours in subjects with normal renal function. It is primarily eliminated in the urine with a small amount of metabolism.

The submission dated December 13, 1996 is a supplement to NDAs 18-703, 19-090, 19-593, 19-675, 20-095, and 20-251 to support the use of Zantac® (all marketed forms) for the treatment of active gastric and duodenal ulcers, maintenance of healing of gastric and duodenal ulcers, GERD, and erosive esophagitis in the pediatric population. The draft labeling provided has been revised in accordance with the 1994 FDA Guidance for Industry on the Content and Format for Pediatric Use Supplements and with 21 CFR 201.57(f)(9)(iii) and (iv), and includes additional pharmacokinetic, pharmacodynamic, and safety information specific to pediatric patients. The pediatric population is defined according to the following terminology: neonates (birth up to 1 month), infants (1 month up to 2 years), children (2 years up to 12 years), and adolescents (12 years up to 16 years). Supportive data was obtained from literature papers and clinical studies.

## Pharmacokinetics of Ranitidine in Pediatric Patients

The studies containing the most relevant and useful information supporting the use of ranitidine in pediatric subjects are reviewed. Detailed summaries of each study can be found in the Appendix.

### Oral Administration

Three studies examining the pharmacokinetics of oral ranitidine are discussed (Table 1). Results are compared in Table 2.

**Table 1. Oral Pediatric Pharmacokinetic Studies Reviewed.**

Study No.	Source	Location in NDA	Page # in Appendix
1	Blumer J, et al. J Pediatrics, 1985;107:301.	Vol 6, pg 2-52.	13
2	Supplemental NDA for Pediatric Labeling, NDA 18-703 Zantac Tablets	Vol 4, Protocol #69-RAN-1149, pg 140-208.	15
3	Mallet E, et al. Eur J Clin Pharmac, 1989;36:641.	Vol 3, pg 333-334.	17

**Table 2. Cross-study comparison of pediatric pharmacokinetic data.**

Study No.	Dose	t <sub>1/2</sub> (hr)	CL (ml/min/m <sup>2</sup> )	Vd (L/kg)	t <sub>max</sub> (hr)	C <sub>max</sub> (ng/ml)	AUC <sub>12hr</sub> (hr*ng/ml)	F
1	150 mg* (tablet)	2.0 (0.5)	455 <sup>§</sup> (192)	2.5 (1.0)	NA	NA	NA	0.48 (0.2)
2	2 mg/kg single dose (syrup)	2.4 (0.5)	NA	NA	1.61 (0.50)	244 (109)	1045 (324)	NA
	2 mg/kg steady state	2.7 (0.5)	NA	NA	1.66 (0.82)	320 (199)	1428 (578)	NA
3	5 mg/kg (iv soln)	2.8 (0.8)	664 (NA)	NA	1.2 (0.4)	476 (164)	NA	NA

The above values are from single-dose studies (except as indicated) and are presented as means±SD.

\*The dose which yielded a serum ranitidine concentration resulting in 90% suppression of gastric acidity was given as 1/4 fractions of a 150 mg tablet.

<sup>§</sup>Units for CL are ml/min/1.73m<sup>2</sup>

Upon examination of Table 2, the mean half-life, t<sub>max</sub>, and C<sub>max</sub> values reported for ranitidine are fairly consistent. However, clearance is considerably lower in Study 1 as compared to Study 3. Unfortunately, values for Vd, AUC, and F (bioavailability) are reported for single studies only. The AUCs from Study 2 indicate lack of significant drug accumulation with repeated dosing.

The differences seen in pharmacokinetic parameters can be attributed to a number of factors including study population, ranitidine formulation, study design, adequacy of experimental/sampling design, etc. The Study Summaries in the Appendix review the adequacy of each study in detail. The reviewer is of the opinion that Study 1 is the most reliable.

The formulations of ranitidine used in the 3 studies were all different. Although the tablets and syrup are considered to be bioequivalent, small differences between these formulations and the iv solution may result in slight variations in values for tmax and Cmax.

All 3 studies suffer from some experimental design or sampling inadequacies. The sampling schemes in most of the studies were marginal with respect to both frequency and duration. Sample sizes were small throughout; most notably, only 4 of the 8 patients in Study 2 had blood drawn, so that the actual evaluable sample was very small. In addition, the validity of the values reported in Study 2 are questionable; for example, tmax is reported as 1.6 hours, however, according to the methods, the first blood sample was not drawn until 3 hours after the dose was given. There were also many deviations from the blood sampling protocol throughout this study. The pharmacokinetics of ranitidine in Study 3 were described using a 1-compartment open model (a 2COM is typically used) which would tend to introduce errors into clearance and half-life determinations.

#### Comparison with adults

One study from the literature and one study performed by the sponsor examining the pharmacokinetics of ranitidine in adults are presented in Table 3.

**Table 3. Oral pharmacokinetics of ranitidine in adults.**

Ref No.	Dose	t <sub>1/2</sub> (hr)	CL (ml/min)	Vd (L/kg)	tmax (hr)	Cmax (ng/ml)	AUC <sub>0-∞</sub> (hr*ng/ml)	F
1	100 mg (tablet)	2.8 (0.6)	1610 (440)	NA	3.0 (1.1)	227 (75)	1180 (350)	0.52 (0.11)
2	150 mg (tablet)	2.3 (0.4)	NA	NA	2.2 (1.2)	502 (154)	2332 (670)	0.60 (0.17)

The above values are from single-dose studies and are presented as means±SD.

Tables 2 and 3 reveal that half-life is consistent when comparing the pediatric data to that of adults. Unfortunately, values for Cl cannot be directly compared due to the different units of measurement used and the inaccessibility of raw data for conversion to a standard format. Volume of distribution is rarely calculated in studies of

1. OCPB review of NDA 18-703, ranitidine 150 mg tablets, July 20, 1982.
2. Van Hecken AM, et al. Brit J Clin Pharmac 1982;14:195.

oral ranitidine pharmacokinetics, however, the one parameter provided in pediatric Study 1 (2.5 L/kg) is not unreasonable in view of the values reported from iv studies in both pediatric studies and adults (see Tables 5 and 6). It is difficult to perform a direct comparison between tmax, Cmax, and AUC as the formulations given to children and adults were not the same. (Study 1 provided tablets but the investigators did not determine these three parameters.) Bioavailabilities of ranitidine ranged from 0.48 to 0.60 where reported. Overall, there are very little pharmacokinetic data for ranitidine in pediatric subjects after oral administration.

#### Intravenous Administration

Six studies examining the pharmacokinetics of ranitidine in pediatric subjects are discussed (Table 4). Results are compared in Table 5.

**Table 4. Intravenous Pediatric Pharmacokinetic Studies Reviewed**

Study No.	Source	Location in NDA	Page # in Appendix
1	Blumer J, et al. J Pediatrics, 1985;107:301.	Vol 6, pg 2-52.	13
5	Leeder JS, et al. Acta Pharm Tox, 1986;59:79.	Vol 4, pg 9.	21
6	Leeder JL, et al. Clin Pharmac Ther, 1985;37:201.	Vol 4, pg 16.	23
7	Wiest, DB et al. Dev Pharmac Ther, 1989;12:7.	Not included.	25
8	Rylance G. In:Perspective on therapeutics in Northern Europe: hyperacidity states, London 1987;52:4.	Vol 4, pg 48-49.	27
9	Protocol RAN-1149.	Vol 4, pg 209-257.	28

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Table 5. Cross-study comparison of pediatric pharmacokinetic data.

Study No.	Dose	$t_{1/2}$ (hr)	CL (ml/min/kg)	Vd (L/kg)	AUC <sub>0-∞</sub> (hr*ng/ml)
1	0.3-2.1 mg/kg	1.8 (0.3)	795* (334)	2.3 (0.9)	NA
5	1.25 or 2.5 mg/kg <6 yr	2.2 (2.1)	11.4 (6.9)	1.3 (0.8)	NA
	6-11.9 yr	2.1 (1.0)	9.0 (3.4)	1.1 (0.5)	NA
	>12 yr	1.7 (0.5)	9.9 (3.0)	1.0 (0.3)	NA
6	2.5 mg/kg 6-10 yr	2.0 (0.7)	9.5 (3.2)	1.5 (0.33)	NA
	11-16 yr	1.6 (0.2)	10.7 (2.8)	1.4 (0.45)	NA
7	1.5 mg/kg	2.1 (1.3)	13.9 (10.0)	1.6 (1.0)	NA
8	1 mg/kg	2.4 (0.9)	10.2 (4.8)	1.9 (1.0)	NA
9	1 mg/kg Neonates (n=1)	4.7	2.2	0.9	7636
	Infants (n=10)	2.4 (0.7)	11.7 (6.3)	2.3 (1.4)	1982 (1440)
	Children (n=5)	2.0 (0.7)	13.7 (3.3)	2.3 (0.9)	1295 (392)
	Adolescents (n=1)	1.9	10.7	1.8	NA

The above values are from single-dose studies and are presented as means±SD.  
 \*CL is reported as ml/min/1.73m<sup>2</sup>

Table 5 reveals that values for half-life and clearance are consistent among all ages of the pediatric population with the exception of 1 neonate in Study 9, who had a much longer half-life and lower clearance. This is not surprising in view of the underdeveloped hepatic and renal capacities in neonates. Glomerular filtration rate is low at birth and is known to increase sharply after the first 2 weeks of life.<sup>3</sup> Fontana et al<sup>4</sup> reported a mean half-life of 3.45±0.31 hr and a mean plasma clearance of 5.02±0.46 ml/kg/min in a study which examined the pharmacokinetics of ranitidine in 27 newborns (18-27 hr) with bloody vomitus. Study 9 also reports values for renal clearance among the 4 pediatric subgroups (see Appendix, Study Summaries). Note

3. Guignard JP. J Pediatr 1975;87:268.

4. Fontana M, et al. Arch Dis Child 1993;68:602.

that renal clearance contributes a smaller percentage to total clearance with decreasing age. The AUC values reported in this study also reflect a diminished capacity for ranitidine elimination in the neonate. Parameters for volume of distribution are fairly consistent across the studies examined.

Overall, many of the same deficiencies noted in the design of studies examining oral ranitidine pharmacokinetics are also present in the iv studies. The primary limitation of these reports are the small sample sizes. In addition, most of the studies include patients with unknown diagnoses, unconfirmed "indicated" diagnoses (PUD), or those who were critically ill. However, in general, the subjects included are heterogenous with respect to age and gender (see Study Summaries in Appendix for detailed reviews) and most of the studies provide useful information.

Many of the reports contain very little regarding methodology and pharmacokinetic calculations, and only discuss pharmacokinetic parameters rather than stating them. For example, the authors of Study 1 discuss AUC values after both po and iv dosing, concluding linear pharmacokinetics for ranitidine as evidenced by a positive linear correlation with dose administered, however, no actual AUC values are provided within the paper. Studies 5 and 6 are provided as abstracts only, a format which necessitates brevity. The sampling schemes are only marginally adequate in Studies 5, 6, and 9 and there is a high degree of variability for some of the parameters. Once again, the reviewer is of the opinion that Study 1 is the most reliable and contains the most useful information.

#### Comparison with adults

The pharmacokinetics of ranitidine in adults are presented in Table 6 and are generally consistent with published literature values<sup>7</sup>.

**Table 6. IV pharmacokinetics of ranitidine in adults.**

Ref	Dose*	t <sub>1/2</sub> (hr)	CL <sub>plasma</sub> * (ml/min/kg)	CL <sub>renal</sub> * (ml/min/kg)	Vd* (L/kg)	AUC <sub>0-∞</sub> (ng*hr/ml)
5	150 mg (2.1 mg/kg)	1.73 (0.15)	9.2 (NA)	7.4 (NA)	1.4 (NA)	3934 (588)
6	100 mg (1.4 mg/kg)	2.0 (0.2)	10.8 (NA)	7.6 (NA)	1.5 (NA)	2240 (320)

The above values are from single-dose studies and are presented as means±SD.  
\*Values normalized per 70 kg man.

5. Van Hecken AM, et al. Brit J Clin Pharmac 1982;14:195.

6. OCPB review of NDA 18-703, ranitidine 150 mg tablets, July 20, 1982.

7. Roberts CJC. Clin Pharmacokin 1984;9:211.

Upon examination of the pharmacokinetic data for the pediatric subjects and adults, it can be observed that values for half-life, clearance, and volume of distribution are relatively consistent among all of the studies presented. Once again, the primary exception are the parameters reported for the neonate. Interestingly, the AUC values tend to be higher in adults, however, the variability in the pediatric data is high. Overall, the pharmacokinetic parameters reported from the studies performed in pediatric subjects and adults are very similar.

### Pharmacodynamics of ranitidine

#### Pediatric Subjects

Results of pharmacodynamic assessments are presented in Table 7. Detailed methodology can be located in the Appendix (Study Summaries).

**Table 7. Pharmacodynamic data in pediatric subjects.**

	Dose	Result
Study 1	0.13 to 0.8 mg/kg iv	$C_{90\%}^* = 40$ to 60 ng/ml
Study 3	5 mg/kg po (iv form.)	<100 ng/ml results in pH<4.0, which occurs 9 hr after the dose
Study 4	2 mg/kg po (syrup)	Gastric pH<2.5 in 33% of patients with serum drug levels ranging from 18-331 ng/ml. No drug levels reported for patients with gastric pH>2.5
Study 8	1 mg/kg iv	2/20 subjects failed to produce gastric pH>3.5 with ranitidine conc>60 ng/ml over 6 hr
Study 9	1 mg/kg iv	Of 10 patients with gastric pH≤2.0 prior to drug therapy, 2 had no acid suppression and the remaining 8 had variable response

\*Serum ranitidine concentration needed to inhibit baseline gastric acid secretion by ≥90%

No formal pharmacokinetic/pharmacodynamic modeling was performed in any of the studies listed above. Pharmacodynamic response was quite variable among individuals across studies, with many subjects exhibiting complete lack of response, even after achieving serum ranitidine concentrations shown to suppress 90% of gastric acid secretion in subjects from Study 1. The large interindividual variability in gastric acid suppression among the studies can likely be attributed to different patient diagnoses and the pharmacodynamic endpoints implemented. For example, subjects in Study 4 had no gastrointestinal indications while those in Studies 8 and 9 were critically ill. Furthermore, all of the studies, except for Study 1, implemented arbitrary pharmacodynamic endpoints and these were based on the subject's condition.